Department of Managed Health Care

MAXIMUS

CALIFORNIA DEPARTMENT OF MANAGED HEALTH CARE

Review of Lyme Disease Related Independent Medical Reviews 1/1/01 to 6/30/04 and Research on the Diagnosis and Treatment of Lyme Disease

OVERVIEW

The Department of Managed Health Care (DMHC) requested MAXIMUS Center for Health Dispute Resolution to provide a synopsis and review of disputed treatments resolved through the IMR program through June 30, 2004 involving diagnostic and treatment disputes for diagnosed or suspected Lyme disease and complications. In addition, DMHC requested an assessment of prevailing contentions regarding the efficacy of diagnostic standards and treatment options.

MAXIMUS CHDR's review was completed by a board certified internist who specializes in the research and treatment of Lyme disease in conjunction with MAXIMUS CHDR staff. The results of this review demonstrated some patterns in California Independent Medical Reviews involving the treatment of Lyme disease and in MAXIMUS CHDR's decision rationale. Concerning the treatment of Lyme disease the results of our review indicate that although there is some controversy over the appropriate treatment of Lyme disease there is evidence-based literature supporting a standard of care.

As part of the request DMHC provided a number of discussion points, which are addressed throughout the following narrative. In addition, the citations to the literature and other works referenced below can be found on the works cited page following the narrative.

LYME DISEASE RELATED INDEPENDENT MEDICAL REVIEWS

Since January 2001, MAXIMUS CHDR has completed 19 independent medical reviews (IMRs) related to Lyme disease. Sixteen of the Lyme disease IMRs involved requests for long-term antibiotics - either oral or intravenous. Two of the IMRs involved requests for treatment with an out-of-plan provider – one of these two IMRs was re-reviewed because it was determined the complete medical record was not submitted during the initial review period. Set forth below is a detailed description and analysis of the types of Lyme disease related IMRs that have been reviewed.

Lyme Disease IMR Volume and Results

During the time period of this study 19 requests related to the treatment of Lyme disease were reviewed. Of the 19 IMRs, the Health Plan denials were upheld in 18 IMRs and overturned in one instance. The medical necessity standard of review was applied in 18 of the IMRs. In 17 of the medical necessity IMRs one Medical Professional Reviewer (MPR) was utilized with three MPRs being utilized in one of the medical necessity IMRs. One IMR was reviewed under the experimental/investigational standard of review. The overturned IMR was reviewed under the medical necessity standard of review.

The 19 IMRs involving Lyme disease were generated from six different California Health Plans. However, four of the Health Plans only had Lyme disease related IMRs in 2001. Only two California Health Plans had Lyme disease related IMRs from January 2002 through June 2004. The highest volume of Lyme disease IMRs arose in 2001 with a total of eight IMRs with one of the IMRs being a re-review. The 2001 re-review occurred because additional relevant medical records were submitted after completion of the initial review The lowest volume arose in 2002

with a total of three IMRs. The projected total volume for Lyme disease related IMRs in 2004 is four.

Types of Lyme Disease IMRs

Set forth below is a detailed review of the Lyme disease related IMRs by year. Although the IMRs are categorized as "Lyme disease related IMRs", it must be noted that none of the 19 IMRs involved a patient with a confirmed diagnosis of Lyme disease who had not yet received an initial course of antibiotic therapy. The majority of IMRs involved enrollees with diagnoses of "Chronic Lyme disease" or "Late Stage Lyme disease" or "Chronic Lyme disease with Babesiosis co-infection". Moreover, almost all IMRs involved enrollees who had previously received treatment with long-term antibiotic therapy. Graphs detailing the information set forth below are contained in Attachment C-2 of this document.

2001

In 2001, there were seven initial IMRs involving Lyme disease and one re-review based upon submission of additional relevant medical records after completion of the initial review. Five of the IMRs involved requests for continued or re-treatment of either oral or intravenous antibiotics. Two of the IMRs involved requests for treatment with non-contracted providers. All seven IMRs were upheld. In all seven IMRs each enrollee had already received long-term (greater than 90 days) courses of antibiotics without evidence of objective improvement in their symptoms. In some instances enrollees had been receiving daily antibiotics for greater than a year without improvement in their symptoms. In three of the five IMRs involving requests for antibiotics, the medical records submitted did not demonstrate findings consistent with a diagnosis of Lyme disease. In the two IMRs requesting services from a non-contracted provider, it was determined the enrollees were being treated by appropriate providers who were knowledgeable in the diagnosis and treatment of Lyme disease and that there was no evidence indicating the requested referrals were medically necessary.

2002

In 2002, there were three IMRs involving Lyme disease. Each of the IMRs involved requests for antibiotics. Two of the IMRs were upheld and one was overturned. The overturned IMR involved a request for antibiotics for the treatment of Babesiosis. The information submitted did not demonstrate the enrollee had received an initial or repeat 7 to 10 day course of antibiotics. Based upon this information the reviewer determined that a 7 to 10 day course of the requested antibiotics was medically indicated. The two upheld IMRs involved requests for long-term (greater than three months) antibiotics. The IMRs were upheld because of a lack of scientific evidence demonstrating the requested therapy was effective or beneficial in treatment of the medical conditions at issue.

2003

In 2003, there were six IMRs involving Lyme disease. All six IMRs were upheld. Five of the IMRs were reviewed under the medical necessity standard of review and one IMR was reviewed under the experimental/investigational standard of review. All six IMRs involved requests for long-term (greater than three months) antibiotics. In five of the six IMRs the medical records submitted did not demonstrate findings consistent with a diagnosis of Lyme disease. In all six of the IMRs each enrollee had already received long-term (greater than three months) courses of antibiotics without evidence of objective improvement in their symptoms. In some instances enrollees had been receiving daily antibiotics for greater than a year without improvement in their

symptoms. The IMRs were upheld because of a lack of scientific evidence demonstrating the requested therapy was effective or beneficial in treatment of the medical conditions at issue.

January 2004 through June 2004

From 1/1/04 through 6/30/04 there were two IMRs involving Lyme disease. Both IMRs were upheld. Both IMRs involved requests for long-term (greater than three months) of antibiotics. In one IMR the medical records submitted did not demonstrate findings consistent with a diagnosis of Lyme disease. Both enrollees had previously been treated with long-term (greater than three months) antibiotics without objective improvement in their condition. One of the enrollees had received over two years of antibiotic therapy without improvement in the enrollee's condition.

Health Plan Volumes

Attachment C-1 to this document contains a table demonstrating individual Health Plan volumes for Lymes disease related IMRs for January 1, 2001 thru June 30, 2004.

LYME DISEASE: DIAGNOSIS AND TREATMENT

According to the United States Department of Health and Human Services National Institutes of Health (NIH), Lyme disease was first recognized in 1975 after researchers investigated an occurrence of large numbers of children who were being diagnosed with juvenile rheumatoid arthritis in Lyme, Connecticut. Upon investigation, researchers discovered a majority of the affected children played and lived near wooded areas where ticks live. It was also determined that initial symptoms began in the summer months, which is the height of tick season. A number of the patients reported having a skin rash immediately prior to developing arthritis. Many of the children also related being bitten by a tick at the rash site. Further investigation revealed deer ticks infected with a spiral-shaped bacterium or spirochete were responsible for the arthritis outbreak in Lyme, Connecticut. Set forth below is a discussion and analysis of literature and guidelines regarding the diagnosis and treatment of Lyme disease.

Diagnosing Lyme Disease

The diagnosis of Lyme disease is made at one of two stages – either early or late. In both stages, the diagnosis is primarily made on clinical grounds. In early stage disease, generally the history consists of a patient who lives in an area where Lyme disease has been reported (disease may not be endemic to the area) and presents primarily in the months of April through October. Typical patient presentation includes fever, headache, arthralgia (joint pain), neck stiffness, fatigue, nausea, and/or chills. All symptoms need not be present. These acute symptoms are usually associated with a macular, erythematous, nonpruritic (sometimes painful) expanding rash of at least five centimeters in diameter. The area of the rash may vary depending upon the area of the tick bite; however, a known tick bite is not necessary for diagnosis. Other manifestations of early Lyme disease include facial nerve palsy and/or first-degree heart block (interference with the normal transmission of electrical impulses through the conducting system of the heart). The above findings may occur from 24-hours to two weeks following inoculation by the tick. In addition, the above presentation is adequate to make a diagnosis of Lye disease and begin treatment.

The laboratory diagnosis of early-stage Lyme disease is not necessary if clinical evidence is strong. The direct detection of the spirochete is difficult. The spirochete may be cultured from the Erythema Migrans (EM) skin lesion or from synovial fluid; however, this is not standard practice. The Center for Disease Control (CDC) recommends a two stage serologic test using ELISA and Western blot. If the ELISA is positive or equivocal, a Western blot assay should be performed. If the ELISA is negative, a Western blot assay is not necessary. The serologic assays take several days and may not be practical in the treatment of early-stage disease. Furthermore, there is a small set of patients who may test positive and never had exposure to the spirochete. In addition, in early-stage disease, the titer may be negative as a result of lack of time for the antibody response.

Criteria for a positive IgM response in the ELISA assay is two of three bands positive with a positive IgG response of five to ten bands. The IgM antibody response is not entirely specific for Lyme disease. Other diseases such as Ehrlichia or Epstein-Barr virus may cause a positive response. The IgM response is only valid for the first month of infection, following which there is seroconversion to an IgG response. It is important to note the serologic markers may remain positive for a lifetime.

Late-stage Lyme disease manifests as neurologic, cardiac or arthritic complications. Neurologic complications include radiculoneuritis (inflammation of the spinal nerve roots), subacute encephalitis, myelopathy, cranial neuropathy, sensory neuropathy, cognitive dysfunction, and meningitis. Symptoms include headache, neck pain, memory loss, paresthesia, muscle weakness, and loss of reflexes. These findings present typically several weeks after the tick bite and inoculation with the spirochete.

Cardiac complications associated with late-stage disease involve second and third degree heart block. These can present weeks after initial infection. Cardiomyopathy and heart failure are not a manifestation of Lyme disease.

The arthritic findings are reactive usually monoarticular, affecting the large joints with pain, effusion, and limited range of motion. The findings may be self-limited but may not resolve for several months if left untreated.

In late-stage disease, the serologic assay is typically positive for an ELISA IgG response and a positive Western blot. CSF or synovial fluid analysis may be positive for the above. Direct culture is very difficult and PCR analysis remains experimental.

Recommended Laboratory Testing

The Food and Drug Administration's (FDA) recommendations for blood testing are consistent with the recommendation of the Center for Disease Control (CDC). As discussed, the diagnosis of Lyme disease is clinical based upon epidemiology, patient history and examination. Serum testing for Lyme disease may be utilized as an adjunct to clinical presentation. Serology may be negative in early disease. Importantly, there is a background of immune positivity in the general population without exposure to Lyme disease. Furthermore, a positive test does not necessarily imply active disease and serology may remain positive for an extended time period.

For the above reasons, the FDA continues to recommend a two test approach. The first test is an assay to detect total class specific antibodies using enzyme-linked immunosorbent technology (ELISA). Criteria for a positive IgM response are the presence of two of three bands (23, 39 or 41-kDa) Criteria for a positive IgG response are the presence of five of ten bands (18, 23, 28, 30, 39, 41, 45, 58, 66 or 93-kDa). IgM levels usually peak within three to six weeks after infection. IgG levels are detectable several weeks to months or years following infection. A negative result indicates no serologic evidence of Borrelia burgdorferi. A positive or equivocal test should be followed by a Western blot assay. Western blot is more specific, secondary to detection of Bb antigens after electrophoresis. A negative Western blot implies no serologic evidence for Lyme disease; however, if suspicion for disease is high a repeat test may be performed two to four weeks later. Although helpful, the above tests are limited as they may remain positive regardless of a patient's disease status and therefore do not necessarily signify or correlate with active disease.

Serologic positivity helps in the diagnosis of Lyme disease but in and of itself is not diagnostic. Tests results alone should not be used to make clinical decisions regarding treatment options. Several new assays, including a rapid test for detection of Borrelia, are now available. These assays use recombinant proteins as serologic assays. Their specificity and sensitivity has not been clearly established and the FDA, CDC and other authorities continue to recommend the two-step approach of ELISA and Western blot. Other testing that is not considered standard of care includes PCR testing, use of a peptide V1sE in an ELISA assay, and culture of Borrelia burgdorferi.

Other Diagnostic and Imaging Studies

The diagnosis of Lyme disease may be supported with positive CSF fluid findings. These include a positive Western blot, elevated protein, and possibly white blood cells in the fluid. SPECT scanning, MRI, and CT have been utilized as imaging methods; however, they require further study because positive findings are part of a broad differential of demyelinating diseases. Furthermore, the specificity and sensitivity are low for all of these studies. Moreover, the diagnosis of Lyme disease cannot be made solely on the basis of positive findings with these techniques.

The diagnosis of Lyme arthritis may be supported with an analysis of the synovial fluid. The findings consist of a reactive/inflammatory inflammatory response with a positive Western blot and or PCR (if available). Radiographs or MRI of the affected joint are not helpful.

There are no conclusive imaging studies to detect the presence of Lyme disease. Xenon (133) regional cerebral blood flow studies have demonstrated flow reductions in the white matter of the posterior temporal and parietal lobes bilaterally. This has been correlated with deficits in memory function and visuospatial organization. PET scanning shows hypometabolism in the temporal lobe. These findings correlate with defects in memory function. However, these remain observational findings without establishing any clear diagnostic pattern.

SPECT scanning sows areas of hypoperfusion in the white matter of the frontal subcortical and cortical structures; however, specificity and sensitivity have not been established and this should not be used to make a diagnosis of Lyme encephalopathy or central nervous system involvement.

MRI and CT reveal nonspecific white matter abnormalities which are neither sensitive nor specific for Lyme disease.

Treatment of Lyme Disease

The only known effective evidenced-based treatment for Lyme disease has been established by the Infectious Diseases Society of America. No other treatment regimens have been established as effective in double blinded, placebo-controlled trials. Set forth below is an outline of standard of care for the treatment of Lyme disease.

Early Infection:

- Adults: Doxycycline, 100mg orally twice a day for 21 to 30 days; Amoxicillin 500mg three times a day for 21 to 30 days. Alternatives for patients who have allergies to the above would be cefuroxime 500mg twice a day for 21 to 30 days and Erythromycin 150mg four times a day for 21 to 30 days.
- Children: Amoxicillin 250mg three times a day or 20mg/kg a day for 21 to 30 days. Alternatives for patients who have allergies are cefuroxime 125mg twice a day for 21 to 30 days
- Arthritis: Doxycycline 100mg twice a day for 30 to 60 days and Amoxicillin 500mg four times a day for 30 to 60 days or Ceftriaxone 2gm intravenously everyday for 14 to 28 days and Penicillin G 20 million units intravenously in four doses day for 14 to 28 days.
- Facial Palsy: Doxycycline 100mg twice a day for 30 days or other oral agent.
- First Degree Heart Block: Doxycycline 100mg twice a day or other oral agent.
- High Degree Heart Block: Ceftriaxone 2gm intravenously daily for 14 to 28 days and Penicillin G 20 million units intravenously in four doses daily for 14 to 28 days.

In addition to the above, symptomatic therapy may include use of nonsteroidal anti-inflammatory medication for arthralgias, fever, etc. No other therapies have been proven in double blind, placebo-controlled trials to be effective including hyperbaric oxygen, other antibiotic regimens or durations of therapy, plasmaphoresis, EDTA chelation and others.

Chronic Lyme Disease

There are no evidenced-based criteria for the diagnosis of Chronic Lyme disease. There is a constellation of symptoms consisting of muscle and joint pain, dysesthesia/paresthesia, fatigue, and memory/cognitive loss following Lyme disease. This most likely occurs primarily in untreated cases. This syndrome may be linked to fibromyalgia and/or chronic fatigue syndrome. There is no evidence that Lyme disease leads to these two diagnoses. There are no laboratory markers or imaging studies to confirm the above syndrome and exam findings are frequently minimal. The treatment of the above conditions is symptomatic with anti-inflammatory medications, anti-depressants, and physical therapy. Chronic Lyme disease is not recognized as a diagnostic entity.

Evidence Basis for the Treatment of Lyme Disease

Two studies providing evidence basis for the treatment of Lyme disease are Klempner MS, et al. *N Engl J Med*, 2001 Jul;345(2) and Krupp LB, et al. *Neurology*, 2003 Jun;60.

The study by Klempner, et al. was a double blind, placebo-controlled trial enrolling 129 patients for treatment with 30 days of Ceftriaxone followed by 60 days of oral Doxycycline or a respective placebo. Outcome measures included a quality of life questionnaire, laboratory testing of serum and CSF fluid for Borrelia antibody positivity and patient adverse events. The study was stopped by the safety and monitoring board because data from the first 107 patients indicated a high likelihood there was no significant difference between the placebo and experimental group in treatment efficacy and because of a significant level of adverse events. The study included patients who had a documented history of Lyme disease and had not received long-term therapy. Prior to institution of the study, patients reported significant impairment of their health related to quality of life including chronic musculoskeletal pain and neurocognitive symptoms. In these patients there was no significant difference between the treatment group and the placebo group in clinical response to treatment. In addition, a significant number of adverse reactions in the treatment group including two serious adverse events were reported.

The study by Krupp, et al. was a single center, double blind, placebo-controlled trial of 55 patients with Lyme disease and persistent symptoms of fatigue for six months or more after antibiotic therapy. As measured by a questionnaire, the patients in the treatment group showed a significant difference in improved fatigue symptoms. No beneficial effect was observed for cognitive function and there was no change in laboratory measure of infection. There were a significant number of adverse events with four of the events resulting in hospitalization. Based upon the results of this study, the authors could not recommend extended antibiotic therapy.

The study by Klempner utilized a different measure of symptom assessment than the Krupp study, but both studies had similar results. The Krupp study investigated fatigue, which is a difficult subjective symptom to measure accurately. There was a significant level of adverse events in both studies leading the authors to conclude any benefit of extended antibiotic therapy did not outweigh the risk of treatment particularly because of the lack of clinical efficacy of extended therapy.

Neither study demonstrated any improvement in cognitive function or musculoskeletal pain. Although the Krupp study found improvement in fatigue and the Klempner study had no such finding, the Klempner study did not use fatigue specifically as an end point and fatigue is a difficult, subjective symptom to measure accurately.

Both studies reached the same conclusion – there is no benefit to extended antibiotic therapy in this group of patients and there is a significant level of adverse events associated with this therapy. Further, both studies demonstrated a lack of laboratory evidence for persistent Borrelia burgdorferi, co-infection or an active inflammatory process in either the treatment of placebo group.

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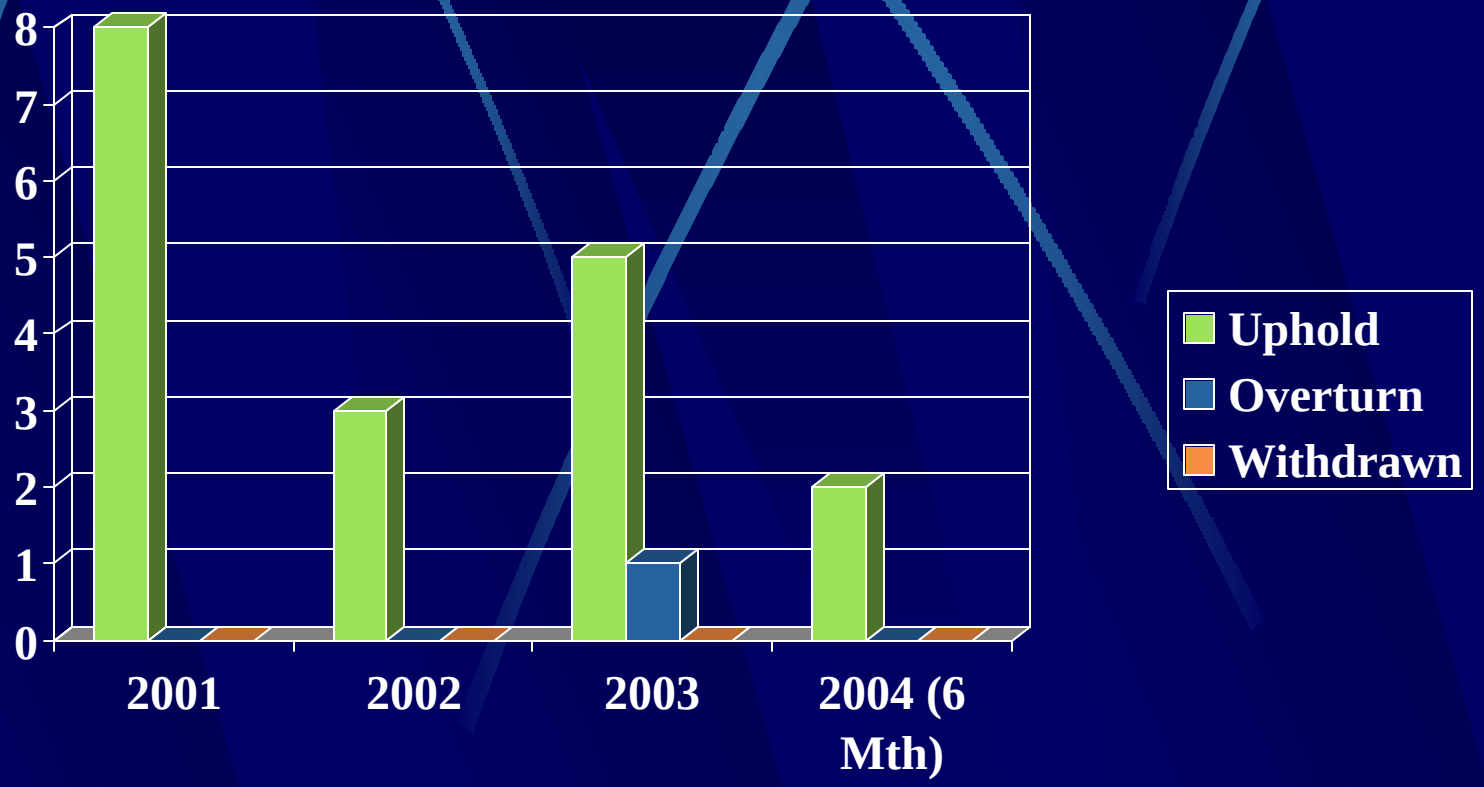
Attachment C-1: Table of Health Plans by Case Year					
HMO	**Case Year**				
Frequency **Percent** **Row Pct** **Col Pct**	**2001**	**2002**	**2003**	**2004**	**Total**
Blue Shield of California	1 5.26 12.50 12.50	2 10.53 25.00 66.67	4 21.05 50.00 66.67	1 5.26 12.50 50.00	8 42.11
Health Net	3 15.79 100.00 37.50	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	3 15.79
Health Plan of the Redwoods	1 5.26 100.00 12.50	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	1 5.26
Kaiser Foundation Health Plan	1 5.26 100.00 12.50	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	1 5.26
PacifiCare of California	2 10.53 100.00 25.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	0 0.00 0.00 0.00	2 10.53
Blue Cross of California	0 0.00 0.00 0.00	1 5.26 25.00 33.33	2 10.53 50.00 33.33	1 5.26 25.00 50.00	4 21.05
Total	8 42.11	3 15.79	6 31.58	2 10.53	19 100.00

Attachment C-2

Lyme Disease – Decision Rates January 2001 thru June 2004



Lyme Disease Related IMRs by Year